CLAIMS

1. A mutant form of human dihydrofolate reductase which differs from wild-type human dihydrofolate reductase at both amino acid 22 and amino acid 31, wherein the mutant form has an amino acid with a larger volume side chain than leucine at amino acid 22 and an amino acid which having a smaller volume, more hydrophilic side chain than phenylalanine at amino acid 31.

2. The mutant form of human dihydrofolate reductase according to claim 1, wherein the amino acid at amino acid 22 is selected from phenylalanine and tyrosine, and the amino acid at amino acid 31 is selected from alanine, serine and glycine.

3. The mutant form of human dihydrofolate reductase according to claim 1, wherein the amino acid at amino acid 22 is phenylalanine and the amino acid at amino acid 31 is serine.

4. cDNA encoding a mutant form of human dihydrofolate reductase which differs from wild-type human dihydrofolate reductase at both amino acid 22 and amino acid 31, wherein the mutant form has an amino acid with a larger volume side chain than leucine at amino acid 22 and an amino acid which having a smaller volume, more hydrophilic side chain than phenylalanine at amino acid 31.

5. The cDNA according to claim 4, wherein the amino acid at amino acid 22 is selected from phenylalanine and tyrosine, and the amino acid at amino acid 31 is selected from alanine, serine and glycine.

6. The cDNA according to claim 4, wherein the amino acid at amino acid 22 is phenylalanine and the amino acid at amino acid 31 is serine.

7. A DNA vector comprising DNA encoding a mutant form of human dihydrofolate reductase which differs from wild-type human dihydrofolate reductase at both amino acid 22 and amino acid 31, wherein the mutant form has an amino acid with a larger

volume side chain than leucine at amino acid 22 and an amino acid which having a smaller volume more hydrophilic side chain than phenylalanine at amino acid 31.

8. A mammalian cell which produces a mutant form of human dihydrofolate reductase which differs from wild-type human dihydrofolate reductase at both amino acid 22 and amino acid 31, wherein the mutant form has an amino acid with a larger volume side chain than leucine at amino acid 22 and an amino acid which having a smaller volume more hydrophilic side chain than phenylalanine at amino acid 31 inserted into a site which is not essential for replication of the vector.

9. The mammalian cell of claim 8, wherein the cell is a hematopoietic cell.

10. The mammalian cell of claim 9, wherein the cell is a peripheral blood stem cell.

11. The mammalian cell of claim 11, wherein the amino acid at amino acid 22 is selected from phenylalanine and tyrosine, and the amino acid at amino acid 31 is selected from alanine, serine and glycine.

12. A method for reducing the toxic effects of antifolate therapy on human cells comprising the step of introducing into the cells an expressible mutant form of human dihydrofolate reductase which differs from wild-type human dihydrofolate reductase at both amino acid 22 and amino acid 31, wherein the mutant form has an amino acid with a larger volume side chain than leucine at amino acid 22 and an amino acid which having a smaller volume more hydrophilic side chain than phenylalanine at amino acid 31.

13. The method according to claim 12, wherein the amino acid at amino acid 22 is selected from phenylalanine and tyrosine, and the amino acid at amino acid 31 is selected from alanine, serine and glycine.

14. The method according to claim 12, wherein the amino acid at amino acid 22 is phenylalanine and the amino acid at amino acid 31 is serine.

15. The method of claim 12, wherein the antifolate is methotrexate.

16. A method for reducing the toxic effects of antifolate therapy in a human patient, comprising the steps of

(a) obtaining hematopoietic cells from the patient;

(b) transducing into the hematopoietic cells an expressible mutant form of human dihydrofolate reductase which differs from wild-type human dihydrofolate reductase at both amino acid 22 and amino acid 31, wherein the mutant form has an amino acid with a larger volume side chain than leucine at amino acid 22 and an amino acid which having a smaller volume, more hydrophilic side chain than phenylalanine at amino acid 31; and

(c) returning the transduced cells to the human patient.

17. The method according to claim 16, wherein the amino acid at amino acid 22 is selected from phenylalanine and tyrosine, and the amino acid at amino acid 31 is selected from alanine, serine and glycine.

18. The method according to claim 16, wherein the amino acid at amino acid 22 is phenylalanine and the amino acid at amino acid 31 is serine.

19. The method of claim 16, wherein the antifolate is methotrexate.

20. A method for selecting among clones for clones expressing a non-selectable gene, comprising the steps of:

(a) inserting the non-selectable gene into a DNA vector comprising DNA encoding a mutant form of human dihydrofolate reductase which differs from wild-type human dihydrofolate reductase at both amino acid 22 and amino acid 31, wherein the mutant form has an amino acid with a larger volume side chain than leucine at amino acid 22 and an amino acid which having a smaller volume more hydrophilic side chain than phenylalanine at amino acid

31 wherein the non-selectable gene is inserted into a site which is not essential for replication of the vector;

(b) introducing the vector containing the non-selectable gene into cells of a type in which the non-selectable gene and the mutant form of dihydrofolate reductase are expressed; and

(c) selecting cells which are resistant to inhibition by antifolates.